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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 08/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/911,904	FARR ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45-54* is/are pending in the application.

4a) Of the above claim(s) *45-51,53 and 54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed May 26, 2004. Currently, claims 45-54 are pending. Claims 45-51, 53-54 have been withdrawn as drawn to non-elected subject matter. Claim 52 is examined on the merits.

2. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

3. Any objections and rejections not reiterated below are hereby withdrawn in view of the newly elected combination of sequences.

4. This action contains new grounds of rejection.

Election/Restrictions

5. Applicant's election of Group IV in Paper filed February 28, 2003 is acknowledged. The response also elected the single combination of nucleic acids C1-C10, namely SEQ ID NO: 115-124. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 31-40 have been withdrawn as directed to non-elected subject matter since the single combination of genes selected contain 10 genes and are found within Table 2. Claims 24-30 have been examined on their merits.

6. In an interview on June 22, 2004, the newly submitted claims were discussed, as they are drawn to numerous combinations of sequences. The examiner acknowledges agreeing to changing the combination of sequences searched for the RCE, however,

did not agree to examine 6 different combinations or method claims. The applicant indicated that Claim 52, SEQ ID NO: 329, 116-118, 121, 123 would be the elected combination. Thus, Claim 52 is under examination.

Each distinct composition would require further search, consideration and is a patentably distinct invention, for the reasons set forth in the restriction requirement.

Accordingly, claims 45-51, 53-54 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Priority

7. This application claims priority to provisional application 60/220,057, filed July 21, 2000.

Drawings

8. The drawings are acceptable.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

9. Claim 52 is rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well established utility.

The claim is drawn to an array comprising a combination of nucleic acids comprising SEQ ID NO: 116, 117, 118, 121, 123 and 329.

The art teaches SEQ ID NO: 116 is C-erb B2; SEQ ID NO: 117 is catalase; SEQ ID NO: 118 is p53; SEQ ID NO: 121 is metallothionein-1 and SEQ ID NO: 123 is multidrug resistant protein-1.

Yokota (Genbank Accession Number AB008451, October 1997) teaches the erbB-2 mRNA from canis familiaris, namely SEQ ID NO: 116. The nucleic acids of Yokota and SEQ ID NO: 116 are 100% identical.

Nakamura et al. (Genbank Accession Number AB012918, October 1999) teaches the mRNA for catalase from canis familiaris, namely SEQ ID NO: 117. The nucleic acids of Nakamura and SEQ ID NO: 117 are 100% identical.

Van Leeuwen et al. (Genbank Accession Number L37107, February 1997) teaches the mRNA from p53 from canis familiaris, namely SEQ ID NO: 118. The nucleic acids of Van Leeuwen and SEQ ID NO: 118 are 100% identical. Van Leeuwen teaches that the findings indicate that the involvement of the p53 gene in the genesis of canine tumors is in a way comparable to that of human tumors.

Kobayashi et al (Genbank Accession Number D84397, June 1999) teaches the mRNA for metallothionein-1 from canis familiaris, namely SEQ ID NO: 121. The nucleic acids of Kobayashi and SEQ ID NO: 121 are 100% identical.

Puel et al. (Genbank Accession Number AF045016, February 1998) teaches the mRNA from MDR1 from canis familiaris, namely SEQ ID NO: 123. The nucleic acids of Puel and SEQ ID NO: 123 are 100% identical.

The prior art does not teach or suggest SE QID NO: 329, directed to an EST asserted by the specification to be useful because it is upregulated with etoposide, caffeine and aspirin.

The art supports the conclusion that many genes are irrelevant in gene microarray assays. As Li et al (J. Theoretical Biology (2002) 219:513-551) note "The presence of this power law function prevents an intrinsic cutoff point between "important" genes and "irrelevant" genes (see abstract)." Li continues in the text to note that "In a typical microarray experiment, however, the problem is not that one does not put enough genes on a chip, but rather having too many genes (see page 539, column 1)." Li discusses the analysis by "fold change" when a gene's expression level changed from one ocndition to another by several folds larger than a preset threshold, that gene is kept for further study. Fold change approach does not include sample size information and is not rigorous from a statistical point of view (page 540, col. 1). Li teaches that fold change approach requires a pre-determined threshold so as to determine whether the expression level difference between two conditions that is considered to be "different enough." This concept that genes whose expression does not change is irrelevant is not limited to Li. Ding et al (Bioinformatics (2003) 19(10):1259-66) notes "A two-way ordering of gene expression data can force irrelevant genes toward the middle in the ordering and can thus be discarded (See abstract)." So Ding expressly indicates that genes without change in expression profiling (and Ding's preferred embodiment is cancer genes) should be discarded. Ding notes at page 1259 that in a selection from thousands of genes, 50 are sufficient. Thus, the overwhelming state of the art supports the position that many genes are irrelevant, that genes whose expression does not change are noise, and that these irrelevant genes are so

insignificant that ideally they are not placed on the arrays or used at all. Therefore, it is unclear that the data provided is indicative of toxicologically relevant nucleic acids.

The instant specification asserts that the claimed arrays are useful for toxicological screening. The response filed May 26, 2004 points to Table 11 and Figure 2 to support the assertion as useful for toxicology screening. The assertion that the array may be used in toxicology screening methods is not specific or substantial. First, with respect to c-erb B-2; catalase, metallothionein 1, MDR1, and p53, Table 11, appears to show the fold induction in the presence of acetaminophen, erythromycin , estradiol and methotrexate. It is not clear that the fold induction between the various genes and compounds is significant. The instant specification does not appear to set forth a pre-determined threshold for the analysis as indicated by Li to be essential. An analysis of Table 11 illustrates that each of cerb B-2, catalase, metallothionein 1 and MDR-1 contain both positive and negative fold induction when exposed to acetaminiophen. Thus, it is unclear how these results are associated with toxicology, and furthermore a real world utility.

Moreover, even if the fold induction for these genes were considered significant, it is unclear how the skilled artisan would use this information in a real world context of use. The specification and the art fail to teach the skilled artisan how to use the information to diagnose a disease, for example. The fact that drugs or compounds change expression of various genes is not unexpected. The specification has not taught the skilled artisan how to use this array comprising a combination of genes other than studying the properties of the claimed product itself or the mechanisms in which the material is involved. The specification simply provides no guidance as to how to interpret the results that might be seen using the claimed microarray-based gene expression assay.

Finally, with respect to well established utility, the specification nor the response has asserted a well established utility for the array comprising known genes. If applicant knows of a well established utility for the claimed array, applicant is invited to assert such a utility on the record for consideration and review.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claim 52 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claim 52 is drawn to an array comprising a combination of toxicologically relevant canine nucleic acid molecules comprising SEQ ID NO: 116, 117, 118, 121, 123 and 329. The invention is an class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

The art teaches SEQ ID NO: 116 is C-erb B2; SEQ ID NO: 117 is catalase; SEQ ID NO: 118 is p53; SEQ ID NO: 121 is metallothionein-1 and SEQ ID NO: 123 is multidrug resistant protein-1.

Yokota (Genbank Accession Number AB008451, October 1997) teaches the erbB-2 mRNA from canis familiaris, namely SEQ ID NO: 116. The nucleic acids of Yokota and SEQ ID NO: 116 are 100% identical.

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Van Leeuwen et al. (Genbank Accession Number L37107, February 1997) teaches the mRNA from p53 from canis familiaris, namely SEQ ID NO: 118. The nucleic acids of Van Leeuwen and SEQ ID NO: 118 are 100% identical. Van Leeuwen teaches that the findings indicate that the involvement of the p53 gene in the genesis of canine tumors is in a way comparable to that of human tumors.

Kobayashi et al (Genbank Accession Number D84397, June 1999) teaches the mRNA for metallothionein-1 from canis familiaris, namely SEQ ID NO: 121. The nucleic acids of Kobayashi and SEQ ID NO: 121 are 100% identical.

Puel et al. (Genbank Accession Number AF045016, February 1998) teaches the mRNA from MDR1 from canis familiaris, namely SEQ ID NO: 123. The nucleic acids of Puel and SEQ ID NO: 123 are 100% identical.

Guidance in the Specification and Working Examples

The specification fails to teach the toxicologically relevance of SEQ ID NO: 116, 117, 118, 121, 123 and 329. The specification provides no evidence that each of these sequences are toxicologically relevant. Table 11 provides information about fold induction for canine genes in a canine array.

C-erb B-2 appears to have a fold induction from between –1.1 and 2 using acetaminiophen, erythromycin, estradiol and methotrexate. Similarly, catalse ranges from –1.6 to 1.6; metallothionein-1 from –1.5 to 3.1; multidrug resistant protein-1 from –1.5 to 1.9; and p53 from 1 to 2.1.

The specification further teaches in Table 9 (page 153) CTP1D which corresponds with SEQ ID NO: 329 is upregulated with etoposide, caffeine and aspirin.

The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied. First, it is not entirely

clear what constitute a toxicologically relevant canine nucleic acid. The nucleic acids, have been treated with various toxicologically relevant compounds and analysis was performed. However, it is unclear whether the slight variation between fold induction is significant to constitute a toxicologically relevant canine nucleic acid.

The art supports the conclusion that many genes are irrelevant in gene microarray assays. As Li et al (J. Theoretical Biology (2002) 219:513-551) note "The presence of this power law function prevents an intrinsic cutoff point between "important" genes and "irrelevant" genes (see abstract)." Li continues in the text to note that "In a typical microarray experiment, however, the problem is not that one does not put enough genes on a chip, but rather having too many genes (see page 539, column 1)." Li discusses the analysis by "fold change" when a gene's expression level changed from one ocndition to another by several folds larger than a preset threshold, that gene is kept for further study. Fold change approach does not include sample size information and is not rigorous from a statistical point of view (page 540, col. 1). Li teaches that fold change approach requires a pre-determined threshold so as to determine whether the expression level difference between two conditions that is considered to be "different enough." This concept that genes whose expression does not change is irrelevant is not limited to Li. Ding et al (Bioinformatics (2003) 19(10):1259-66) notes "A two-way ordering of gene expression data can force irrelevant genes toward the middle in the ordering and can thus be discarded (See abstract)." So Ding expressly indicates that genes without change in expression profiling (and Ding's preferred embodiment is cancer genes) should be discarded. Ding notes at page 1259 that in a selection from thousands of genes, 50 are sufficient. Thus, the overwhelming state of the art supports the position that many genes are irrelevant, that genes whose expression does not change are noise, and that these irrelevant genes are so

insignificant that ideally they are not placed on the arrays or used at all. Therefore, it is unclear that the data provided is indicative of toxicologically relevant nucleic acids. The instant specification does not appear to set forth a pre-determined threshold for the analysis. An analysis of Table 11 illustrates that each of cerb B-2, catalase, metallothionein 1 and MDR-1 contain both positive and negative fold induction when exposed to acetaminiophen. Thus, it is unclear how these results are associated with toxicology, and furthermore a real world utility

Specifically with SEQ ID NO: 329, the specification teaches upregulation with etoposide, caffeine and aspirin. It is unclear how upregulation with etoposide, caffeine and aspirin constitute toxicologically relevant canine nucleic acids. It is not clear that aspirin and caffeine are toxic to canines. Further, an skilled artisan would not know how to use these nucleic acids given the information that they are toxicologically relevant. The specification nor the art teach the skilled artisan how to use toxicologically relevant nucleic acids with out undue experimentation. In the event that SEQ ID NO: 329 is deemed toxicologically relevant, it is unclear how this information may be used. Often times, over expression of particular genes are associated with diseases, such as cancers. Thus the ordinary artisan may perform an assay for detecting a predisposition to cancers by detecting an over expression of a particular gene in a sample. Here, however, it is unclear once the skilled artisan knows that caffeine upregulates SEQ ID NO: 329, for example how this information will be used. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the art and the specification fail to provide any information about how to use the nucleic acids as toxicologically relevant canine nucleic acids. Further, the prior art and the specification provides insufficient guidance how to use these nucleic acids in such a manner. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 112-Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claim 52 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn, in part to nucleic acid molecules comprising SEQ ID NO: 329. The specification teaches SEQ ID NO: 329 is not a full length gene or cDNA.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2b 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2b 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...' required a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention". In analyzing whether the written description requirement is met for a genus claim, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, Applicant has defined only a fragment of a nucleic acid sequence. Applicant has not disclosed any genomic DNA sequences and particularly has not disclosed any intron sequences or regulatory sequences. Accordingly, Applicants have not adequately disclosed the relevant identifying characteristics of a representative number of species within the claimed genus.

This rejection may be easily overcome by amending the claim to require a nucleic acid molecule consisting of SE QID NO: 329.

Conclusion

12. No claims allowable.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (571) 272-0782.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

J. Goldberg

Jeanine Goldberg
Patent Examiner
August 9, 2004